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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,658	BRADLEY ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,67 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,67 and 68* is/are rejected.

7)☒ Claim(s) *1 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Office action is in response to an amendment filed on January 27, 2003. Claims 1-66 were pending, with claims 18-66 withdrawn from consideration. Applicants cancelled claims 18-66, amended claims 7-11 and 17 and added new claims 66 and 67.

2. Applicants' amendment overcame the rejections of claims 7-11 and 17 under 35 U.S.C. 112, second paragraph. Applicants' arguments regarding rejections of claims 15 and 16 were considered but were found not persuasive (see Response to Arguments below).

3. In view of applicants arguments the following rejections are withdrawn: rejection of claims 1-12, 15 and 16 under 35 U.S.C. 1029b) over Lockhart et al., rejection of claim 13 under 35 U.S.C. 103 over Lockhart et al. and Anderson, and rejection of claims 14 and 17 under 35 U.S.C. 103 over Lockhart et al.

4. This Office action is made non-final because of new grounds for rejection.

Response to Arguments

Applicants' arguments regarding rejection of claims 15 and 16 under 35 U.S.C. 112, second paragraph, were considered but were not found persuasive. The terms "substantially an entire chromosome" and "substantially an entire genome" were used in these claims. The reason for the rejection of these two terms as indefinite is that it is not clear what percentage of a chromosome or a genome would be considered as "substantially entire". Would it be 60, 80, 95%?

Applicants argue that the term "substantially" is used to describe a particular characteristic of the invention and cite MPEP 2173.05(b)(D). Applicants argue that "substantially" is a descriptive term commonly used in patent claims to avoid strict numerical boundaries. According to Applicants: ""Substantially" is given its ordinary meaning and is construed in light of the written description and file history as understood by one of ordinary skill in the art." (Response, page 6, top

paragraph). Applicants argue further that from page 3, lines 25-31 of the specification one would understand what is meant by a "substantially an entire chromosome".

However, MPEP 2173.02 cautions

"**MPEP 2173.02**

Examples of claim language which have been held to be indefinite set forth in MPEP § 2173.05(d) are fact specific and should not be applied as per se rules. The test for definiteness under 35 U.S.C. 112, second paragraph is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)."

The following description is given on page 3, lines 25-31:

"In one embodiment, the target nucleic acid consists essentially of DNA derived from a human. The sample of target genomic nucleic acid can comprise sequences representing a defined fragment of a chromosome or substantially one or more entire chromosomes. The sample of target genomic nucleic acid can comprise sequences representing substantially an entire genome. In an alternative embodiment, the DNA from which the target or the probe nucleic acid is derived from a mammal, such as a mouse or a human genome."

From the above description one cannot conclude what percentage of a chromosome or genome would be considered as "substantially entire". Again, MPEP 2173.02:

MPEP 2173.02

If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph would be appropriate. See Morton Int 'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

In the case of these two phrases, one cannot determine metes and bounds of the phrase "substantially entire", therefore rejection of claims 15 and 16 is maintained.

Claim Objections

5. Claim 1 is objected to as having an inconsistency between the preamble and method steps. The inconsistency arises from the fact that the preamble states that genomic DNA target is hybridized to a nucleic acid probe (singular), whereas in the method steps a plurality of probes are provided.

6. Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 6 depends from claim 3, which contains a limitation of the labeled fragments being no more than 100 bases long, whereas in claim 6 the labeled fragments are from 30 to 150 bases long.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-17, 67 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 is indefinite because the claim does not recite a final process step which clearly relates back to the preamble. The preamble states that the method is for generating a molecular profile of genomic DNA, but the final process step is "contacting the genomic nucleic acids of step (b) with the immobilized probes of step (a) under conditions allowing hybridization of the target nucleic acid to the probe nucleic acid". Therefore, it is unclear as to whether the claim is intended to be limited to a method of generating a molecular profile

or a method of hybridization.

B) Claim 10 is indefinite over the recitation of "target genomic nucleic acid is prepared using a procedure comprising fragmentation ... by DNAse enzyme digestion of the segments". The only segments mentioned in claim 1 are present in the probes (step a), therefore it is not clear how fragmentation of the probes results in the preparation of target genomic DNA.

C) Claim 15 is indefinite over the recitation of "substantially an entire chromosome". It is not clear what percentage of the total chromosome would be considered as "substantially entire", and the specification does not provide a definition or examples.

D) Claim 16 is indefinite over the recitation of "substantially an entire genome". It is not clear what percentage of the total genome would be considered as "substantially entire", and the specification does not provide a definition or examples.

E) Claim 67 is indefinite over the recitation of "nucleic acid comprises representing at least one chromosome". It is not clear what is the part representing at least one chromosome.

F) Claim 68 is indefinite over the recitation of "nucleic acid comprises representing a complete genome". It is not clear what is the part representing a complete genome.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 2, 6, 7, 12-17, 67 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al. (Human Mol. Genetics, vol. 8, pp. 459-470, March 1999; cited in the IDS).

Regarding claims 1, 2, 6, 7, 14-17, 67 and 68, Huang et al. teach profiling of a methylation pattern of genomic DNA in breast cancer cells. Genomic DNA from six human breast cancer cell lines was digested with the restriction enzyme MseI, which generates fragments with lengths ranging from 100-200 base pairs (bp). The fragments were ligated to linkers, treated with BstUI restriction enzyme and amplified. The amplified DNA fragments were labeled with ^{32}P. (Fig. 2; page 460, second and third paragraphs; page 468, second paragraph).

The amplified DNA fragments were then hybridized to an array of 276 CpG island probes (Fig. 2; page 468, third paragraph).

Regarding claim 12 and 13, Huang et al. teach stringent hybridization conditions at a temperature of 65° C (page 468, third paragraph).

11. Claims 1-8, 12, 14-17, 67 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Cronin et al. (Human Mutation, vol. 7, pp. 244-255, 1996).

Regarding claims 1-8, Cronin et al. teach detection of cystic fibrosis mutations by hybridization of target nucleic acids to an array of immobilized probes. Two types of arrays were used: one had probes which allowed identification of differences from the wild type sequences in exon 11, the second array contained 1480 probes for detection of deletions, insertions and base substitutions (Abstract; page 245, 246). Genomic DNA used in the hybridization experiments was amplified, labeled with fluorescein by amplification with fluorescein-labeled nucleotides, then the amplification products were fragmented with uracil-N-glycosylase. The fragmented PCR products were 20-60 bp long. The labeled, fragmented Target DNA was hybridized with the arrays, and the images were obtained using a confocal epifluorescent microscope (page 247).

Regarding claim 12, Cronin et al. teach stringent hybridization conditions (page 245, second column).

Regarding claims 14-17, 67 and 68, Cronin et al. teach genomic samples obtained from human CFTR patients (page 247, first paragraph).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. as applied to claim 8 above, and further in view of Waggoner et al. (U. S. Patent No. 5,268,486).

A) Claim 9 is drawn to the label comprising Cy3 or Cy5.

B) Cronin et al. teach fluorescent labels, but do not teach Cy3 or Cy5.

C) Waggoner et al. teach luminescent cyanine dyes, including Cy3 and Cy 5 (col. 19, formula at the bottom; claim 8; Cy3 has m=1, Cy5 has m=2). the dyes can be used to label nucleic acids (col. 2, lines 58-61; col. 4, lines 29-35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the cyanine dyes of Waggoner et al. in the method of Cronin et al. The motivation to do so, provided by Waggoner et al., would have been that cyanine dyes were used for detecting mixtures of components because they had a wide range of excitation and emission wavelengths (col. 4, lines 36-49).

14. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. as applied to claim 1 above, and further in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1981).

A) Claim 10 is drawn to fragmentation of genomic DNA to sizes smaller than 200 bases by DNAse digestion.

B) Cronin et al. do not teach fragmentation of DNA by DNAse digestion.

C) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNAse I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used DNAse I digestion of Anderson to fragment genomic target DNA in the method of Cronin et al. The motivation to do so, provided by Anderson, would have been that DNAse I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNAse I in the reaction (page 3019, first two paragraphs).

15. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. as applied to claim 1 above, and further in view of Ordahl et al. (Nucl. Acids Res., vol. 3, pp. 2985-2999, 1976) and Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1981).

A) Claim 11 is drawn to fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNAse digestion.

B) Cronin et al. do not teach fragmentation of genomic DNA to sizes smaller than 200 bases by applying shear forces to fragment genomic DNA followed DNAse digestion.

C) Ordahl et al. teach fragmentation of genomic DNA in preparation for DNA hybridization experiments. Ordahl et al. teach that it is advantageous to use DNA fragments of less than 500 bp in hybridization experiments (page 2985, first paragraph). Ordahl et al. teach that DNA fragmented in French press had an average size of 230 base pairs (Abstract; page 2986; Fig. 4). Ordahl et al. do not teach DNAse I fragmentation after shearing.

D) Anderson teaches fragmentation of genomic DNA to sizes below 200 base pairs by digestion with 2.2 ng or more of DNAse I (Figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used shearing of Ordahl et al. and DNAse I digestion of Anderson to fragment genomic target DNA in the method of Cronin et al. The motivation to do so, provided by Ordahl et al. and Anderson, would have been that it was advantageous to use short DNA fragments in hybridization (Ordahl, p. 2885, first paragraph) and that DNAse I digestion was sequence-independent and the sizes distribution obtained could be regulated by regulating the amount of DNAse I in the reaction (Anderson, page 3019, first two paragraphs).

16. Claim 13 rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. as applied to claim 12 above, and further in view of Anderson et al. ("Nucleic acid hybridization, a practical approach", IRL Press, Oxford-Washington DC, pp. 93-95, 1985).

A) Claim 13 is drawn to the stringent hybridization conditions comprising a temperature of about 60-65° C.

B) Cronin et al. teach stringent hybridization conditions of incubation at 30° C and washing at 25-30° C for probes which are 15 bp long (page 247, second column, first paragraph). Cronin et al. do not teach a temperature of 60 to 65° C.

C) Anderson et al. teach that temperature and salt concentration of the washing solution determine which hybrids will be dissociated, and is usually chosen to be at 5-20° C below Tm for well-matched hybrids (page 95, first paragraph). Therefore the wash temperature will depend on the probe's length, GC content and ionic strength of the solution, since Tm depends on these variables.

It would have been *prima facie* obvious to one of ordinary skill in the art to adjust the temperature of the stringent wash solution according to Anderson et al. when considering probes of different lengths and compositions than the probes used by Cronin et al. The motivation to do would have been that adjusting hybridization conditions allowed discrimination between matched and mismatched probe-target complexes.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

April 23, 2003

Teresa Strzelecka, Ph. D.

Patent Examiner

Teresa Strzelecka

4/23/03